OXYGEN-OZONE THERAPY IN THE PREVENTION OF THE OXIDATIVE CELLULAR DAMAGE: AN ANTIAGEING HYPOTHESIS

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Since many years the role of reactive oxygen species (**ROS**) in the acute and chronic diseases represented the topic of numerous scientific papers. Indeed, the oxidative damage to DNA, RNA, protein and cell membranes that physiologically occurs during the ageing process and the partial protection exerted by the cell defence systems represent well-known processes. On the other hand, in various pathological conditions the main problem is related to a rapid increase in the cellular **ROS** concentration that exceeds the capacity of the cell to eliminate them. Normally, **ROS** derived from the oxygen reduction during the biochemical pathways of the cell energy production systems (*Gershman, Science, 119: 623-626, 1954*). In some pathological conditions **ROS** could increase either for a primitive defect of the cell defence system or following an overproductions derived either from the cell death or apoptosis phenomena. Nevertheless, the role of the oxidative stress in the induction of apoptosis is well known and the oxidation of glutathione represents an early event in the course of apoptosis. Recent data dealt on the pro-oxidative activity of CuZn superoxide dismutase (**SOD**) and nitroxide **SOD**-mimics. **SOD** is unique in being present in cells and in various experimental systems in a concentration excess over its substrate. If the enzyme or its mimics are present in the oxidized form, they may oxidize various cellular or exogenous substrates (*Offer et al,* FASEB J*, 14(9): 1215-23, 2000*). The natural defenses against ROS could be classified as exogenous or endogenous. The first ones, diet dependent, comprise vitamins, E and C, flavonoids and polyphenols while **SOD**, glutathione peroxidase, catalases are being considered the main endogenous species. The first hypothesis of a positive conditioning induced by low ozone concentrations against the oxidative stress has been recently proposed by Leon Fernandez et al (*Int. Cong. Pharmacol., CPT 2000, Florence, Brit J Clin Pharmaco, July 15-20, 2000*). The theory is based upon the fact the low, non-toxic, ozone doses could raise the efficacy of the endogenous system by increasing the production or the activity of some antioxidant enzymes isoforms. Looking at the ischaemic preconditioning in which is scientifically proved that repetitive brief ischaemia plays an important role in the acquisition of late-phase cardio protection against ischaemia/reperfusion injury in rats (*Yamashita et al, Br J Pharmacol, 131(3): 415-422, 2000*), we can speculate that repetitive brief oxidative stress induced with low ozone doses could ameliorate the cell defences mechanisms against **ROS**. The hypothesis is supported by other data reported by Rao and Shaha (*Free Radic Biol Med, Nov 15; 29 (10): 1015-1027, 2000*) demonstrating the formation of multiple isoforms of glutathione S-transferase after the exposure to H_2O_2. A further evidence of the protective action induced by low ozone concentrations has been proposed by our group (*Re et al, Gen Pharmacol, 32; 245-250, 1999*). Indeed, we proved the reduction of the intracellular calcium at presynaptic levels after the exposure to low ozone doses. The cytosolic calcium could be considered as the common final pathway of the cellular damage, either physiologically or pathologically. A low calcium level represents a further element in supporting the idea of the oxidative cell damage protection either in the chronic or in the acute ageing. We think that the use of ozone in the medical field could represents a useful and safety therapeutic potential in many pathologies actually orphan of adequate pharmacological treatment and in the prevention of the naturally occurring ageing.